Pharmacotherapy of Posttraumatic Stress Disorder: Treatment Options, Long-Term Follow-Up, and Predictors of Outcome

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Posttraumatic stress disorder (PTSD) is a prevalent and disabling condition. Treatment is essential to reduce symptoms, increase the patient's functioning and well-being, and reduce comorbidity with other psychological disorders. Evidence suggests that psychopharmacologic therapy can be effective in PTSD. This article considers clinical data for various pharmacologic treatment options for PTSD; in particular, several recent studies of selective serotonin reuptake inhibitors are examined. The long-term effects of pharmacotherapy and issues concerning patient management are also discussed.

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Posttraumatic stress disorder (PTSD) is a prevalent condition; lifetime prevalence rates of 1.3% to 7.8% have been reported in the community.[1,2] It is a disabling disorder and is associated with a large degree of morbidity. In addition, PTSD is frequently comorbid with other psychological conditions such as depression.[2]

Since the 1980s, when PTSD was first recognized (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition* [DSM-III][3]), relatively few double-blind clinical studies have been carried out to assess the efficacy of drugs in PTSD. However, data from the clinical studies that have been conducted indicate that pharmacologic intervention can be effective in the treatment of PTSD.

Appropriate treatment is essential to reduce symptoms of PTSD and increase the functioning and well-being of the patient. This article examines the pharmacologic treatment options for PTSD that are open to the physician and reviews published clinical trial data. The long-term benefits of pharmacotherapy and issues relating to the management of patients with PTSD are also discussed.

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MANAGEMENT CONSIDERATIONS

Treatment Goals

The physician has 5 main goals when treating PTSD: reducing the core symptoms, improving stress resilience (i.e., helping patients to cope better and to be more resilient), improving quality of life, reducing disability, and reducing comorbidity.

Outcome Assessment

There is no "gold standard" for assessing outcome in PTSD; to date, many different rating scales have been used. This subject is too large to be discussed fully in this paper; however, it is expanded upon in a review by Shalev[4] in this supplement.

In several placebo-controlled studies,[5–10] the Clinical Global Impressions-Improvement scale (CGI-I) score was used. The lowest effect size was seen with brofaromine (0.4) and the highest with phenelzine (0.8). The average score was approximately 0.6, which would be regarded by Cohen[11] as a moderate effect size, while 0.8 would be regarded as moderately strong.

By comparing different scales in 2 studies and looking at effect size, the scale performance can be assessed. In a study of sertraline versus placebo (J.R.T.D., unpublished observations), when looking at the change in score as the variable, effect sizes on the CGI-I (0.51) and the Davidson Trauma Scale (DTS) (0.40) were stronger than those on the CGI-Severity scale (CGI-S) (0.31) and the Clinician-Administered PTSD Scale (CAPS) (0.32). In another study, of fluoxetine,[12] the 8-item Treatment-Outcome PTSD scale (TOP-8) gave the best effect size at endpoint (1.07), followed by the Structured Interview for PTSD (0.96) and the

DTS (0.94). The other scales (CGI-I, CGI-S, and Impact of Event Scale [IES]) gave a medium effect size (0.53–0.59). Thus, there are differences in the ability of scales to distinguish differences in drug-placebo responses.

Compliance

A primary concern when considering pharmacotherapeutic options for PTSD is the patient's willingness to comply with the various demands and inconveniences of the treatment regimen, for example, multiple versus single daily dosing. The choice of drug is going to be dependent, to some extent, on the overall health picture of the patient. There are also issues of mistrust, fear, stigma, sick role and disability, and tolerability of side effects.

Stopping Treatment

Whether the patient's response to treatment is total or just partial should be taken into account when considering stopping therapy. It is also important to assess the patient's attitude toward discontinuing medication; that is, the patient has to be ready and confident. In addition, medication may need to be stopped because of unacceptable side effects. Support for the patient must be available as treatment is discontinued. The physician must be prepared to deal with problems such as discontinuation symptoms or relapse. It is important to discontinue treatment slowly.

PHARMACOLOGIC TREATMENT OPTIONS

Agents studied in double-blind trials of PTSD (in both combat and noncombat trauma patients) and shown to be effective in at least 1 trial include the tricyclic antidepressants amitriptyline and imipramine,[5,6] the irreversible monoamine oxidase inhibitor (MAOI) phenelzine,[6] the reversible MAOI inhibitor brofaromine (which is no longer available),[8] the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline,[9,10,13] and, in one small study, the anticonvulsant lamotrigine.[14]

Furthermore, other agents including paroxetine, fluvoxamine, mirtazapine, nefazodone, moclobemide, carbamazepine, sodium valproate, clonidine, and propranolol have been studied in open-label trials that suggest the efficacy of these agents in PTSD.

Tricyclic Antidepressants

Two 8-week, placebo-controlled studies of tricyclic antidepressants have been carried out, both in male combat veterans with PTSD defined using DSM-III[3] criteria. In the first study, 46 World War II or Vietnam veterans were treated with amitriptyline (50–300 mg/day) or placebo.[5] Amitriptyline was more effective than placebo ($p = .06$); the proportion of patients with a final CGI-I score of 1 or 2 (very much or much improved) was 50% for amitriptyline and 17% for placebo. The second study, by Kosten and coworkers,[6] investigated imipramine (50–300 mg/day) in 60 Vietnam veterans. There was a greater reduction in symptoms in patients treated with imipramine, as shown by decreases in IES scores from baseline (25% for imipramine vs. 5% for placebo). Further, using a global scale, more patients were shown to have improved with imipramine (65%) than with placebo (28%).

These major controlled studies of tricyclic antidepressants in PTSD show that, in war veterans, PTSD can respond meaningfully to pharmacotherapy to a greater extent than to placebo.

Monoamine Oxidase Inhibitors

Three placebo-controlled studies and 1 open-label study of MAOIs in PTSD have been published. In the study by Kosten and colleagues,[6] the efficacy of phenelzine (15–75 mg/day) was examined. A 45% decrease from baseline in the IES score was observed with phenelzine (compared with 5% for placebo), showing its efficacy in the treatment of combat veterans with PTSD.

Two placebo-controlled trials with brofaromine (titrated up to 150 mg/day) have been reported: one 12-week study in the United States[7] and one 14-week study in Europe.[8] In the U.S. study,[7] significant reductions in symptoms (assessed using the CAPS) were observed for both brofaromine and placebo; however, no significant differences were seen between the treatment groups. The results of the European study[8] differed, depending on the assessment scale reported: a significant difference favoring brofaromine was seen with the CGI-I, but not with the CAPS. The main difference between these studies was the patient population; most (approximately 60%) of the patients in the U.S. study were combat veterans, whereas in the European study, patients were mostly civilians.

Moclobemide is the only reversible selective MAO-A inhibitor currently available. One open-label study[15] of this drug has been carried out in the United Kingdom in 20 patients who met DSM-III-R criteria for PTSD. This trial suggested that moclobemide is effective in the treatment of PTSD since at the end of 12 weeks of treatment, 11 patients no longer met the criteria for PTSD.

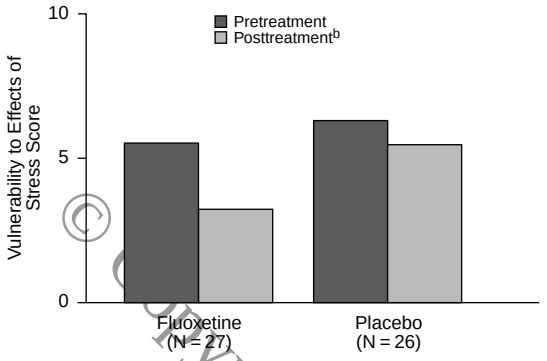
Selective Serotonin Reuptake Inhibitors

Several studies of SSRIs in PTSD have been reported: 4 placebo-controlled studies and 3 open-label studies.

In a 5-week study of fluoxetine in 64 men and women with PTSD (veteran and civilian subjects),[13] the overall CAPS score was significantly reduced from baseline in fluoxetine-treated patients relative to placebo-treated patients in a completer analysis ($p = .016$). Although a substantial number of patients left treatment early, no intent-to-treat analysis was performed.

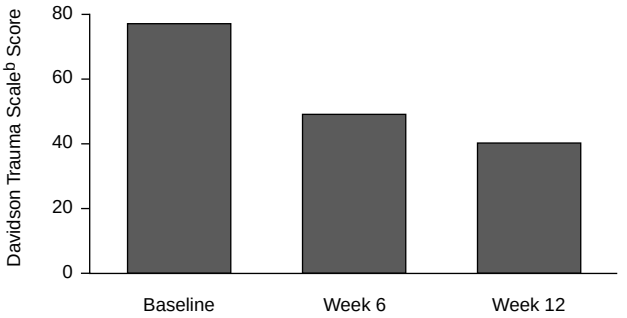
A 12-week, double-blind study[10] compared fluoxetine (up to 60 mg/day) and placebo in 53 civilians with PTSD (DSM-III-R criteria). The results showed that 85% of patients taking fluoxetine and 62% taking placebo had a

Figure 1. The Strengthening of Resilience by a Selective Serotonin Reuptake Inhibitor (SSRI) in Posttraumatic Stress Disorder (PTSD)[a]



[a]Data from Connor et al.[10]
[b]$p < .05$, fluoxetine vs. placebo at posttreatment.

Figure 2. Davidson Trauma Scale Scores After 6 and 12 Weeks of Treatment With Paroxetine (N = 17)[a]



[a]Data from Marshall et al.[17]
[b]For Davidson Trauma Scale, see Davidson et al.[18] A lower score denotes improvement.

Duke Global Rating for PTSD (Duke) improvement score of 1 or 2 (very much or much improved). Using the more strict criterion of a Duke improvement score of 1 (very much improved), the response rates were lower (59% for fluoxetine and 19% for placebo). In addition, high end-state function, i.e., good outcome on interview, self-rating, and disability rating scales, showed a response rate for fluoxetine of 41% and a placebo response rate of 4%.

In the same study, the vulnerability of patients to the effects of stress was measured on a self-rating scale. By the end of treatment, subjects receiving fluoxetine were less upset by stressful events in everyday life than those in the placebo group (Figure 1). Using the Short Form 36, fluoxetine was also shown to have a favorable effect on quality of life in a subset of this study population.[16]

A placebo comparison of sertraline in PTSD has recently been conducted.[9] In this 12-week trial, Baker and coworkers[9] studied nearly 200 adult outpatients with PTSD (DSM-III-R). Preliminary data showed a significantly larger decrease in the CAPS total score for sertraline (43%) than for placebo (31%) ($p < .05$). Similarly, a significantly greater decrease in the DTS was seen for sertraline (39%) than for placebo (24%) ($p < .01$). Using the Quality of Life Enjoyment and Satisfaction Questionnaire, sertraline therapy was shown to have positive effects on quality of life.

An open-label study of paroxetine[17] has been conducted in 19 civilians with DSM-III-R PTSD. Over a 12-week period, a drop in DTS score of approximately 50% (Figure 2) and a reduction in IES score of approximately 40% were seen, indicating paroxetine efficacy in PTSD. The results of this study also indicated that people who had been exposed to any kind of trauma in childhood were less likely to respond to therapy. This is contrary to previous observations in a fluoxetine study, but it is difficult to interpret this finding owing to differences in study designs.

A 10-week, open-label study of fluvoxamine (dose range, 100–250 mg/day)[19] has been conducted in 10 combat veterans with chronic PTSD (DSM-III-R criteria). The results showed that fluvoxamine was effective in the treatment of PTSD symptoms.

More recently, an 8-week, open-label study of fluvoxamine (up to 200 mg/day)[20] was conducted in 15 civilian patients with PTSD (DSM-IV[21] criteria). Overall, 64% of patients who completed the study had a Duke improvement score of 1 or 2 at study end and were classed as responders. Also, significant reductions in mean scores for all efficacy scales used (including the TOP-8, DTS, and IES) were observed at study end. These results indicate that fluvoxamine may be effective in non–combat-related PTSD.

5-HT_2 Antagonist

Results of 6 open-label trials of the serotonin-2 (5-HT_2) antagonist nefazodone in combat veterans and civilian trauma patients have been reported.[22] The response rates (defined as a drop in severity on the primary assessment scale) in the combat veteran population studies (33%–50%) were generally lower than in the civilian studies (59%–60%). Thus, it is likely that patients derived from Veterans Affairs medical center populations have more severe PTSD than those in studies of noncombat trauma patients.

Anticonvulsants

One small placebo-controlled study and 2 small open-label studies of anticonvulsant agents have been carried out.

A recent 12-week, double-blind, placebo-controlled trial of lamotrigine (up to a maximum dose of 500 mg/day if tolerated)[14] was conducted in 15 patients with PTSD. The response rate in patients receiving active treatment was twice as high as that for patients receiving placebo (50% vs. 25%, respectively). However, the potentially serious skin rash means that a slow dose escalation is required for this drug, which may be slow to act.

Table 1. Long- and Short-Term Outcomes in PTSD at 15-Month Follow-Up After Treatment With Fluoxetine for Either 6 Months and More or Less Than 6 Months

Assessment Scale (range of possible scores)[a]	Treatment ≥ 6 Months	Treatment < 6 Months
Clinical Global Impressions-Severity (1 to 7)	2.5	4.1
Davidson Trauma Scale (0 to 136)	36.9	91.6[b]
Sheehan Disability Scale (0 to 30)	7.9	20.3[c]

[a]Higher score denotes greater symptoms/disability.
[b]p = .001.
[c]p = .003.

Table 2. Long- and Short-Term Response to Fluoxetine

Assessment Scale (range of possible scores)[a]	Baseline	Month 3	Month 15
Clinical Global Impressions-Severity (1 to 7)	4.4	3.5	3.2
Davidson Trauma Scale (0 to 136)	88.2	64.1	61.4
Sheehan Disability Scale (0 to 30)	21.1	21.9	13.4[b]

[a]Higher score denotes greater symptoms/disability.
[b]p < .0001 for month 15 vs. baseline.

Open-label studies of carbamazepine[23] and sodium valproate[24] have been conducted in combat veterans, mainly survivors of the Vietnam war, who met DSM-III or DSM-III-R criteria for PTSD. The carbamazepine study[23] showed that 7 of 10 patients had a response of "moderately" to "very much" improved following treatment. Similar results were seen in a small (N = 16) study of sodium valproate[24]; PTSD symptoms improved in the majority of patients. Although positive results have been observed with these compounds, there have not been any double-blind trials with either of these agents.

LONG-TERM EFFECTS OF PHARMACOTHERAPY

Prolonged treatment has been studied in 2 fluoxetine trials. In the first (J.R.T.D., unpublished data, March 1999), patients were followed up to 15 months to determine the benefit of continued treatment. Table 1 shows outcomes for patients who received treatment for either 6 months and longer or less than 6 months. At follow-up, patients who remained on fluoxetine treatment for 6 months had lower scores on the CGI-S, DTS, and Sheehan Disability Scale compared with patients who received shorter-term treatment. Thus, patients treated for 6 months or more showed greater improvements in symptoms and disability compared with those treated for a shorter duration. This study also suggests that more severely symptomatic patients may need special encouragement to stay in treatment. It is an important therapeutic as well as research task to determine how best to motivate those most in need of treatment to stay in treatment. The issue of motivation, the sense of being precontemplators (i.e., those not fully committed to, or engaged in, treatment) on a stages-of-change continuum, has been discussed by Beitman et al.,[25] who found that an otherwise effective benzodiazepine drug in panic disorder was ineffective in the precontemplator group. A similar study in PTSD patients might be revealing.

The second trial, a naturalistic follow-up study (J.R.T.D., unpublished data, March 1999), found that patients who responded well after 3 months of treatment generally continued to do well on follow-up at month 15 (Table 2). On the Sheehan Disability Scale, there was no change in score at month 3, but at month 15 a reduction in score was observed. This suggests that in some patients with PTSD, it takes longer for the disability and the daily functioning scores to improve than for some of the PTSD symptoms to improve.

Predictors of outcome at 15 months after 3 months of treatment were also investigated, including baseline symptoms, gender, types of trauma, number of traumas, and clinical response at weeks 1 and 2. Logistic regression showed that only 1 variable was significant as a predictor of long-term outcome, and this was how well patients had done in the short term, i.e., the month 3 score. For each 10-point increase in the DTS at month 3, there is a 29% lower chance of being a responder at month 15.

CONCLUSION

PTSD is a disabling condition that requires prompt and appropriate treatment. Disability symptoms in PTSD appear to improve more slowly than other symptoms. However, benefits of treatment may be felt in many patients at 15 months. Importantly, the response at 3 months has been identified as a predictor of long-term outcome in PTSD.

The SSRIs have been shown to be effective in PTSD, and patients who respond to treatment with an SSRI respond on all 4 symptom clusters, as well as on disability measures and resilience. Anticonvulsant agents and nefazodone show some promise in the treatment of PTSD, and older antidepressants may be particularly useful for combat-induced PTSD. However, since few controlled trials of pharmacologic agents in PTSD have been conducted, further study is required.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others), clonidine (Catapres and others), fluoxetine (Prozac), fluvoxamine (Luvox), lamotrigine (Lamictal), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), propranolol (Inderal and others), sertraline (Zoloft).

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